1,153,670

PATENT SPECIFICATION

NO DRAWINGS

1,153,6

Inventors: GIORGIO FERRARI and CESARE CASAGRANDE

Date of Application and filing Complete Specification: 5 Dec., 1967.
No. 55371/67.
Application made in Belgium (No. 690,792) on 7 Dec., 1966.
Complete Specification Published: 29 May, 1969.

Index at acceptance:—C2 C(3A7V1A4, 3A7V1E2, 3A7V1F2, 3A7V1J3, 3A7V1J1, 3A7V
3A7V3A4, 3A7V3E2, 3A7V3F2, 3A7V3J3, 3A12A4A, 3A1
3A12C5, 3A12A4B, 3A13C6C, 3A13C10F, 3A13C10H, KH186, KH
KH190, KH213, KH214, KH247, KH25Y, KH250, KH251, KH
KH32Y, KH322, KH323, KH34Y, KH342, KH36Y, KH364, KH
KH62X, KH650, KH672, 186—189—190, KN186, KN189, KN
KN213, KN214, KN247, KN25Y, KN250, KN251, KN30Y, KN
KN322, KN323, KN34Y, KN342, KN36Y, KN364, KN366, KN
KN584, KN62X, KN678, 186—189—190, LQ186, LQ189, LQ190, LQ
LQ214, LQ22Y, LQ220, LQ226, LQ247, LQ25Y, LQ250, LQ251, LQ
LQ29X, LQ30Y, LQ32Y, LQ323, LQ36Y, LQ364, LQ366, LQ368, LQ
LQ620, LQ628, LQ634, LQ65D, LQ678, 186—189—190)

Int. Cl.:—C 07 d 57/04

COMPLETE SPECIFICATION

ERRATUM

SPECIFICATION NO. 1,153,670

Page 1, for Index at Acceptance C2C only read:-

(3A7V1A4, 3A7V1E2, 3A7V1F2, 3A7V1J1, 3A7V1J3, 3A7V1L, 3A7V3A4, 3A7V3E2, 3A
3A7V3J3, 3A12A4A, 3A12A4B, 3A12B7, 3A12C5, 3A13C6C, 3A13C10F, 3A13C10H, 21
22Y, 220, 226, 247, 25Y, 250, 251, 29Y, 29X, 30Y, 32Y, 322, 323, 34Y, 342,
364, 366, 367, 368, 491, 584, 62X, 620, 628, 634, 650, 672, 678, 186- 189-
KH, KN, LQ)

THE PATENT OFFICE,
19th December 1969

D 120

in which the pyrrole ring may be unsaturated or saturated, R^1 is a hydrogen atom or a carboxyl or esterified carboxyl group, R^2 is an alkyl, cycloalkyl, aryl, carboxyl, esterified carboxyl, carboxymethyl, esterified carboxymethyl, carboxyamido or substituted carboxyamido group, R^3 is a hydrogen atom or a carboxyl or esterified carboxyl group, or R^2 and R^3 when taken together may form the anhydride group of the corresponding dicarboxylic acid, and salts and addition compounds with pharmacologically acceptable organic or inorganic bases or acids.

In formula (I) above the bonds represented by broken lines may be present, forming a pyrrole ring (5,6-dihydropyrrole [2,1-a] isoquinoline), or absent, constituting a pyrrolidine ring (1,2,3,5,6,10b-hexahydropyrrole [2,1-a] isoquinoline).

The groups represented by R^1, R^2 and R^3 are illustrated in more detail in Table 1.

[*Price 4s. 6d.*]

SEE ERRATA SLIP ATTACHED

1,153,670

PATENT SPECIFICATION

NO DRAWINGS

1,153,670

Inventors: GIORGIO FERRARI and CESARE CASAGRANDE

Date of Application and filing Complete Specification: 5 Dec., 1967.
No. 55371/67.
Application made in Belgium (No. 690,792) on 7 Dec., 1966.
Complete Specification Published: 29 May, 1969.

Index at acceptance:—C2 C(3A7V1A4, 3A7V1E2, 3A7V1F2, 3A7V1J3, 3A7V1J1, 3A7V1L, 3A7V3A4, 3A7V3E2, 3A7V3F2, 3A7V3J3, 3A12A4A, 3A12B7, 3A12C5, 3A12A4B, 3A13C6C, 3A13C10F, 3A13C10H, KH186, KH189, KH190, KH213, KH214, KH247, KH25Y, KH250, KH251, KH30Y, KH32Y, KH322, KH323, KH34Y, KH342, KH36Y, KH364, KH584, KH62X, KH650, KH672, 186—189—190, KN186, KN189, KN190, KN213, KN214, KN247, KN25Y, KN250, KN251, KN30Y, KN32Y, KN322, KN323, KN34Y, KN342, KN36Y, KN364, KN366, KN367, KN584, KN62X, KN678, 186—189—190, LQ186, LQ189, LQ190, LQ213, LQ214, LQ22Y, LQ220, LQ226, LQ247, LQ25Y, LQ250, LQ251, LQ29Y, LQ29X, LQ30Y, LQ32Y, LQ323, LQ36Y, LQ364, LQ366, LQ368, LQ491, LQ620, LQ628, LQ634, LQ65D, LQ678, 186—189—190)

Int. Cl.:—C 07 d 57/04

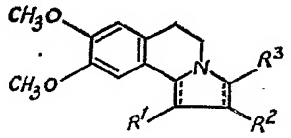
COMPLETE SPECIFICATION

Isoquinoline Derivatives and preparation thereof

We, SIPHAR S.A., a Swiss Body Corporate, of Corso Pestalozzi 9, Lugano, Switzerland, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to heterocyclic compounds, more particularly pyrrole [2,1-a] isoquinoline derivatives. These compounds have interesting therapeutic properties.

In accordance with the present invention there is provided a pyrrole [2,1-a] isoquinoline derivative having the formula:



(I)

in which the pyrrole ring may be unsaturated or saturated, R^1 is a hydrogen atom or a carboxyl or esterified carboxyl group, R^2 is an alkyl, cycloalkyl, aryl, carboxyl, esterified carboxyl, carboxymethyl, esterified carboxymethyl, carboxyamido or substituted carboxyamido group, R^3 is a hydrogen atom or a carboxyl or esterified carboxyl group, or R^2 and R^3 when taken together may form the anhydride group of the corresponding dicarboxylic acid, and salts and addition compounds with pharmacologically acceptable organic or inorganic bases or acids.

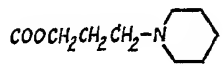
In formula (I) above the bonds represented by broken lines may be present, forming a pyrrole ring (5,6-dihydropyrrole [2,1-a] isoquinoline), or absent, constituting a pyrrolidine ring (1,2,3,5,6,10b-hexahydropyrrole [2,1-a] isoquinoline).

The groups represented by R^1, R^2 and R^3 are illustrated in more detail in Table 1.

[*Price 4s. 6d.*]

SEE ERRATA SLIP ATTACHED

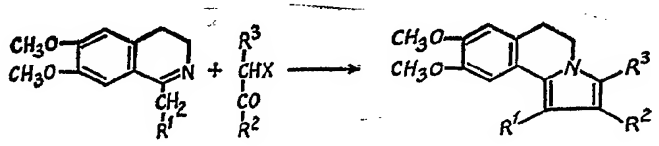
TABLE 1

R_1	R_2	R_3
H	methyl	H
COOH	cyclohexyl	COOH
$COOC_2H_5$	phenyl	$COOC_2H_5$
$COOCH_2CH_2N(CH_3)_2$	COOH	$COOCH_2CH_2N(CH_3)_2$
	$COOC_2H_5$	
	CH_2COOH	
	$CH_2COOC_2H_5$	
	$CONHCH_2CH_2N(C_2H_5)_2$	

The following are preferred compounds according to the present invention:
2 - Phenyl - 5,6 - dihydro - 8,9 - dimethoxypyrrole [2,1-a]isoquinoline - 1 - carboxylic acid;
ethyl 2 - phenyl - 5,6 - dihydro - 8,9 - dimethoxypyrrole [2,1-a]isoquinoline - 1 carboxylate;
dimethylaminoethyl - 2 - phenyl - 5,6 - dihydro - 8,9 - dimethoxypyrrole [2,1-a]-isoquinoline-1-carboxylate;
2 - phenyl - 5,6 - dihydro - 8,9 - dimethoxypyrrole[2,1-a]isoquinoline;
2 - cyclohexyl - 5,6 - dihydro - 8,9 - dimethoxypyrrole[2,1-a]isoquinoline;
2 - phenyl - 1,2,3,5,6,10b - hexahydro - 8,9 - dimethoxypyrrole [2,1-a]isoquinoline;
2 - cyclohexyl - 1,2,3,5,6,10b - hexahydro - 8,9 - dimethoxypyrrole[2,1-a]isoquinoline, and the sulphate and hydrobromide perbromide thereof;
5,6 - dihydro - 8,9 - dimethoxypyrrole[2,1-a]isoquinoline - 2 - carboxylic acid;
ethyl 5,6 - dihydro - 8,9 - dimethoxypyrrole[2,1-a]isoquinoline - 2 - carboxylate;
5,6 - dihydro - 8,9 - dimethoxypyrrole[2,1-a]isoquinoline - 2 - carboxylic acid N - diethylaminoethylamide;
5,6 - dihydro - 8,9 - dimethoxypyrrole [2,1-a]isoquinoline - 2,3 - dicarboxylic acid;
diethyl 5,6 - dihydro - 8,9 - dimethoxypyrrole [2,1-a]isoquinoline - 2,3 - dicarboxylate;
5,6 - dihydro - 8,9 - dimethoxypyrrole [2,1-a]isoquinoline - 2,3 - dicarboxylic acid anhydride;
2 - (N - diethylaminoethyl - carbamyl) - 5,6 - dihydro - 8,9 - dimethoxypyrrole [2,1-a] isoquinoline - 3 - carboxylic acid;
dimethylaminoethyl 2 - methyl - 5,6 - dihydro - 8,9 - dimethoxypyrrole [2,1-a]isoquinoline - 3 - carboxylate; and the hydrochloride thereof;
γ - piperidinopropyl 2 - methyl - 5,6 - dihydro - 8,9 - dimethoxypyrrole [2,1-a] isoquinoline - 3 - carboxylate;
5,6 - dihydro - 8,9 - dimethoxypyrrole [2,1-a] isoquinoline - 2 - acetic acid; and
ethyl 5,6 - dihydro - 8,9 - dimethoxypyrrole [2,1-a] isoquinoline - 2 - acetate.

The invention also includes the salts and addition compounds of the compounds mentioned above with pharmacologically acceptable organic or inorganic bases or acids.

The present invention also provides a process for the preparation of compounds of formula (I) herein, which comprises condensing a substituted α-halocarbonyl compound with an appropriately substituted 3,4-dihydroisoquinoline according to the equation



in which R^1, R^2 and R^3 are as defined hereinabove and X represents a halogen atom (preferably chlorine or bromine), and, if desired, subjecting the cyclisation product so obtained to appropriate transformations of the substituent groups to obtain the desired compound as indicated above, and, if desired, subjecting the compound to catalytic hydrogenation to obtain the corresponding pyrrolidine compound.

In particular, the cyclisation process comprises the reaction of an appropriate halocarbonyl compound, for example, ω-bromoacetophenone of ω-chloroacetophenone, bromomethylcyclohexylketone or chloromethylcyclohexylketone, diethyl chloro-oxal-acetate or bromo-oxalacetate, ethyl γ-chloroacetoacetate or bromo-acetoacetate, ethyl chloropyruvate or bromopyruvate, with 1-methyl-3,4-dihydro-6,7-dimethoxyisoquinoline or with ethyl 3,4-dihydro-6,7-dimethoxy-1-isoquinoline-acetate, preferably in a suitable solvent, such as methyl alcohol or ethyl alcohol or acetone or dioxane, in the presence or absence of a suitable acceptor of hydrohalic acids, such as sodium bicarbonate, potassium carbonate or N,N-dicyclohexylmethylamine, at temperatures between 10°C. and the boiling point of the solvents.

The transformation processes which may be carried out on the substituent groups particularly comprise: the saponification of esters with alkalis by the usual techniques to yield the corresponding acids; the transesterification of esters by suitable amino-alcohols, for example dimethylaminoethanol or γ-piperidinopropanol, in the presence of a suitable catalyst such as for example an alkali alcoholate, by heating to boiling in a suitable inert solvent which allows the lower alcohol formed to be removed by distillation, such as benzene, toluene or xylene; the conversion of esters to amides by reaction with an amine in the presence or absence of a suitable catalyst such as an alkali metal, or an alkali metal amide or alcoholate; the thermal decarboxylation of carboxylic acids by heating to a temperature close to their melting point; the preparation of cyclic anhydrides from vicinal dicarboxylic acids; and the reaction of the anhydride so obtained with an amine.

A preferred process according to the invention is one in which 1-methyl-3,4-dihydro-6,7-dimethoxyisoquinoline is condensed with diethyl chloro-oxalacetate or ethyl chloropyruvate or ethyl γ-chloroacetoacetate, respectively yielding the ethyl esters of 5,6-dihydro-8,9-dimethoxypyrrole [2,1-a] isoquinoline-2,3-dicarboxylic acid or 5,6-dihydro-8,9-dimethoxypyrrole [2,1-a] isoquinoline-2-carboxylic acid or 5,6-dihydro-8,9-dimethoxypyrrole [2,1-a] isoquinoline-2-acetic acid and thereafter the ethyl esters thus obtained are saponified with alkali yielding the corresponding acids.

The processes for the hydrogenation of the cyclisation products particularly consist of hydrogenation in the presence of a catalyst based on platinum, at a temperature between ambient temperature and 80°C. and a hydrogen pressure between 1 and 50 atmospheres, or hydrogenation in the presence of Raney nickel at a temperature between 80° and 150°C. and at a hydrogen pressure of between 80 and 150 atmospheres.

The heterocyclic compounds of the present invention possess hypotensive, sympathicolytic and psychotropic properties, and are thus useful for the treatment of malfunctions of the cardio-circulatory system and also of the nervous system.

The present invention further provides a pharmaceutical composition which comprises, as the active ingredient, a compound of formula (I) herein or a salt or addition compound thereof in admixture with a pharmacologically acceptable carrier.

Amongst suitable pharmaceutical compositions there may be mentioned tablets, capsules, injectable solutions and suppositories.

The invention is further illustrated by the following Examples.

Example 1.

Ethyl 5,6-dihydro-8,9-dimethoxy-pyrrole [2,1-a]-isoquinoline-2-carboxylate.

A mixture of 50 g. of 6,7-dimethoxy-3,4-dihydro-1-methylisoquinoline, 39 g. of ethyl chloropyruvate and 42 g. of sodium bicarbonate in 500 ml. of absolute alcohol is stirred at 35°C for 5 hours.

The mixture is diluted with 1500 ml. of water, and the precipitate is filtered, carefully washed with water and crystallised from alcohol-ligroin. Ethyl 5,6-dihydro-8,9-dimethoxypyrrole [2,1-a]isoquinoline-2-carboxylate of melting point: 111° to 113°C. is thus obtained.

Example 2.

Ethyl 5,6-dihydro-8,9-dimethoxypyrrole [2,1-a] isoquinoline-2-acetate.

On following the procedure of Example 1 but replacing the ethyl chloropyruvate by an equivalent amount of ethyl γ-chloroacetoacetate, ethyl 5,6-dihydro-8,9-dimethoxy-pyrrole [2,1-a] isoquinoline-2-acetate, of melting point: 91° to 93°C. (from alcohol-ligroin) is obtained. The reaction is carried out at 55°C.

EXAMPLE 3.

Ethyl 2-phenyl-5,6-dihydro-8,9-dimethoxypyrrole [2,1-a] isoquinoline-1-carboxylate.

A mixture of 55 g of ethyl 6,7-dimethoxy-3,4-dihydro-1-isoquinoline acetate, 40 g. of ω-bromoacetophenone and 40 g. of sodium bicarbonate in 800 ml. of absolute alcohol is heated to boiling under reflux for 2 hours, with stirring.

The mixture is cooled, and the precipitate is filtered, carefully washed with water and alcohol, and crystallised from ethyl acetate. Ethyl 2-phenyl-5,6-dihydro-8,9-dimethoxypyrrole [2,1-a] isoquinoline-1-carboxylate of melting point 172°C. to 174°C. is thus obtained.

EXAMPLE 4.

Diethyl 5,6-dihydro-8,9-dimethoxypyrrole [2,1-a]isoquinoline 2,3-dicarboxylate.

A mixture of 61.5 g. of 6,7-dimethoxy-3,4-dihydro-1-methyl-isoquinoline, 67 g. of diethyl chloro-oxalacetate and 75 g. of sodium bicarbonate in 500 ml. of absolute alcohol is kept at 50°C. for 2 hours, with stirring.

The mixture is cooled, filtered, and the residue carefully washed with water and recrystallised from alcohol-water. Diethyl 5,6-dihydro-8,9-dimethoxypyrrole [2,1-a] isoquinoline-2,3-dicarboxylate of melting point: 91° to 93°C. is thus obtained.

EXAMPLE 5.

2-Phenyl-5,6-dihydro-8,9-dimethoxypyrrole [2,1-a] isoquinoline.

A mixture of 41 g. of 6,7-dimethoxy-3,4-dihydro-1-methyl-isoquinoline, 40 g. of ω-bromoacetophenone and 40 g. of sodium bicarbonate in 500 ml. of absolute alcohol is heated to boiling under reflux for 3 hours, with stirring. The mixture is cooled, and the precipitate is filtered, carefully washed with water and alcohol, and crystallised from ethyl acetate. 2-Phenyl-5,6-dihydro-8,9-dimethoxy pyrrole [2,1-a] isoquinoline of melting point: 138° to 140°C. is thus obtained.

EXAMPLE 6.

2-Cyclohexyl-5,6-dihydro-8,9-dimethoxypyrrole [1,2-a]isoquinoline.

A mixture of 60 g. of 6,7-dimethoxy-3,4-dihydro-1-methylisoquinoline, 60 g. of bromomethylcyclohexylketone and 60 g of sodium bicarbonate in 400 ml. of alcohol is stirred at 50°C. for 2 hours. The mixture is diluted with an equal volume of water, and the precipitate is filtered off, carefully washed with water and alcohol, and crystallised from ethyl acetate. 2-Cyclohexyl-5,6-dihydro-8,9-dimethoxypyrrole [2,1-a] isoquinoline of melting point: 122° to 124°C. is thus obtained.

EXAMPLE 7.

Dimethylaminoethyl 2-phenyl-5,6-dihydro-8,9-dimethoxypyrrole [2,1-a]isoquinoline-1-carboxylate.

10 ml. of a 13% solution of sodium ethylate in alcohol are added to a solution of 48 g. of ethyl 2-phenyl-5,6-dihydro-8,9-dimethoxypyrrole [2,1-a]isoquinoline-1-carboxylate and 20 g. of dimethylaminoethanol in 600 ml. of toluene.

The mixture is heated to boiling and the alcohol which forms in the reaction is continuously removed by azeotropic distillation in a rectification column.

After 6 hours the mixture is cooled, washed with water, and extracted with 10% acetic acid. The acetic acid extract is rendered alkaline with ammonia and extracted with chloroform.

On evaporating the chloroform and crystallising the residue from ethyl acetate, dimethylaminoethyl-2-phenyl-5,6-dihydro-8,9-dimethoxypyrrole [2,1-a]isoquinoline-1-carboxylate of melting point: 137° to 139°C. is obtained.

EXAMPLE 8.

Dimethylaminoethyl 2-methyl-5,6-dihydro-8,9-dimethoxypyrrole [2,1-a] isoquinoline-3-carboxylate.

On following the procedure of Example 7, but replacing the ethyl 2-phenyl-5,6-dihydro-8,9-dimethoxypyrrole [2,1-a]isoquinoline-1-carboxylate by an equivalent amount (40 g.) of ethyl 2-methyl-5,6-dihydro-8,9-dimethoxypyrrole [2,1-a] isoquinoline-3-carboxylate, dimethylaminoethyl 2-methyl-5,6-dihydro-8,9-dimethoxypyrrole [2,1-a]isoquinoline-3-carboxylate of melting point: 98° to 99°C. (from ligroin) is obtained.

The hydrochloride which is obtained by treating the base, in ether, with anhydrous hydrochloric acid has a melting point of 252° to 255°C. (with decomposition).

EXAMPLE 9.

γ-Piperidinopropyl 2-methyl-5,6-dihydro-8,9-dimethoxypyrrole-[2,1-a]isoquinoline-3-carboxylate.

On following the procedure of Example 8 but replacing the dimethylaminoethanol by an equivalent quantity (31 g.) of γ-piperidinopropanol, γ-piperidinopropyl 2-methyl-5,6-dihydro-8,9-dimethoxypyrrole [2,1-a]isoquinoline-3-carboxylate of melting point: 102° to 104°C. (from ethyl acetate) is obtained.

EXAMPLE 10.

5,6-Dihydro-8,9-dimethoxypyrrole [2,1-a]isoquinoline-2-carboxylic acid N,N-diethylaminoethylamide.

20 g. of ethyl 5,6-dihydro-8,9-dimethoxypyrrole [2,1-a]isoquinoline-2-carboxylate are added to a solution of 1.6 g. of sodium in 40 g. of N,N-diethylethylenediamine. The mixture is heated at 125°C. for 9 hours, the excess amine is evaporated under reduced pressure, the residue is taken up in 10% acetic acid, the solution filtered, and the filtrate rendered alkaline with ammonia and extracted with chloroform. On evaporating the chloroform and recrystallising the residue from toluene, 5,6-dihydro-8,9-dimethoxypyrrole [2,1-a]isoquinoline-2-carboxylic acid N,N-diethylaminoethylamide of melting point: 146° to 148°C. is obtained.

EXAMPLE 11.

5,6-Dihydro-8,9-dimethoxypyrrole [2,1-a] isoquinoline-2-carboxylic acid.

40 g. of ethyl-5,6-dihydro-8,9-dimethoxypyrrole [2,1-a]isoquinoline-2-carboxylate in 800 ml. of 5% alcoholic sodium hydroxide is heated to boiling under reflux for 3 hours. The solvent is evaporated under reduced pressure, the residue taken up in water, and the solution filtered and acidified with acetic acid. The precipitate is filtered off and crystallised from absolute alcohol. 5,6-Dihydro-8,9-dimethoxypyrrole [2,1-a]isoquinoline-2-carboxylic acid of melting point: 232° to 234°C. (with decomposition) is thus obtained.

EXAMPLE 12.

5,6-Dihydro-8,9-dimethoxypyrrole [2,1-a]isoquinoline-2-acetic acid.

On following the procedure of Example 11 but replacing the ethyl-5,6-dihydro-8,9-dimethoxypyrrole [2,1-a]isoquinoline-2-carboxylate by an equivalent quantity (42 g.) of ethyl 5,6-dihydro-8,9-dimethoxypyrrole[2,1-a]isoquinoline-2-acetate, 5,6-dihydro-8,9-dimethoxypyrrole [2,1-a]isoquinoline-2-acetic acid of melting point: 159° to 160°C. (with decomposition) (from alcohol) is obtained.

EXAMPLE 13.

2-Phenyl-5,6-dihydro-8,9-dimethoxypyrrole [2,1-a]isoquinoline-1-carboxylic acid.

40 g. of ethyl 2-phenyl-5,6-dihydro-8,9-dimethoxypyrrole[2,1-a]isoquinoline-1-carboxylate are heated to boiling under reflux with 1600 ml. of 2% alcoholic sodium hydroxide for 2 hours. Finally, the alcohol is evaporated under reduced pressure, the residue is taken up in water, and the solution is filtered and acidified with acetic acid.

On filtering the precipitate and recrystallising from dimethylformamide-alcohol, 2-phenyl-5,6-dihydro-8,9-dimethoxypyrrole[2,1-a]isoquinoline-1-carboxylic acid of melting point: 209° to 211°C. (decomposition) is obtained.

EXAMPLE 14.

5,6-Dihydro-8,9-dimethoxypyrrole [2,1-a]isoquinoline-2,3-dicarboxylic acid.

A solution of 40 g. of diethyl - 5,6 - dihydro - 8,9 - dimethoxypyrrole [2,1-a]-isoquinoline-2,3-dicarboxylate in 1600 ml. of 5% alcoholic sodium hydroxide is heated to boiling under reflux for 2 to 3 hours.

The alcohol is evaporated under reduced presure, the residue is taken up in water, and the solution is filtered and acidified with hydrochloric acid to a pH of 1.

On filtering the precipitate and recrystallising from dimethylformamide-alcohol, 5,6-dihydro-8,9-dimethoxypyrrole [2,1-a]isoquinoline-2,3-dicarboxylic acid of melting point: 229° to 230°C. (with decomposition) is obtained.

EXAMPLE 15.

5,6-Dihydro-8,9-dimethoxypyrrole [2,1-a]isoquinoline-2,3-dicarboxylic acid anhydride.

50 g. of 5,6-dihydro-8,9-dimethoxypyrrole [2,1-a] isoquinoline-2,3-dicarboxylic acid in a mixture of 150 ml. of acetic anhydride and 1 l. of toluene are heated to boiling under reflux for 3 hours.

On cooling and filtering the precipitate, 5,6-dihydro-8,9-dimethoxypyrrole [2,1-a]-isoquinoline-2,3-dicarboxylic acid anhydride of melting point: 239° to 240°C. is obtained.

EXAMPLE 16.

2(N,N-Diethylaminoethylcarbamyl)-5,6-dihydro-8,9-dimethoxypyrrole-[2,1-a]isoquinoline-3-carboxylic acid.

A mixture of 40 g. of 5,6-dihydro-8,9-dimethoxypyrrole [2,1-a]isoquinoline-2,3-dicarboxylic acid anhydride and 16 g. of N,N-diethylethylenediamine in 800 ml. of benzene is heated to boiling under reflux for 5 to 6 hours. The mixture is cooled, and the precipitate which has formed is filtered off, washed with hot ethyl acetate and recrystallised from benzene.

2 - (N,N - Diethylaminoethylcarbamyl)5,6 - dihydro - 8,9 - dimethoxypyrrole [2,1-a]isoquinoline-3-carboxylic acid of melting point: 168° to 170°C. is obtained.

EXAMPLE 17.

5,6-Dihydro-8,9-dimethoxypyrrole [2,1-a]isoquinoline-2-carboxylic acid N,N-diethylaminoethylamide.

On heating 2-(N,N-diethylaminoethylcarbamyl)-5,6-dihydro-8,9-dimethoxypyrrole [2,1-a] isoquinoline-3-carboxylic acid to 190°C. until evolution of carbon dioxide is complete (about 1½ hours), cooling, washing the product with water and recrystallising it from toluene, 5,6-dihydro-8,9-dimethoxypyrrole [2,1-a]isoquinoline-2-carboxylic acid N,N-diethylaminoethylamide of melting point: 146° to 148°C. is obtained.

EXAMPLE 18.

2-Phenyl-1,2,3,5,6,10b-hexahydro-8,9-dimethoxypyrrole [2,1-a] isoquinoline.

20 g. of 2-phenyl-5,6-dihydro-8,9-dimethoxypyrrole [2,1-a]isoquinoline in 1600 ml. of glacial acetic acid are hydrogenated at ambient temperature, under a pressure of 3 to 20 atmospheres, in the presence of 3 g. of platinum oxide; after 25 to 30 hours the hydrogenation is stopped, the catalyst filtered off, the solvent evaporated under reduced pressure down to a small volume, and the residue diluted with water and filtered. On rendering the filtrate alkaline with ammonia, 2-phenyl-1,2,3,5,6,10b-hexahydro-8,9-dimethoxypyrrole [2,1-a]isoquinoline is obtained; this has a melting point of 121° to 123°C. when recrystallised from ligroin.

EXAMPLE 19.

2-Cyclohexyl-1,2,3,5,6,10b-hexahydro-8,9-dimethoxypyrrole [2,1-a]isoquinoline and 2-cyclohexyl-5,6-dihydro-8,9-dimethoxypyrrole [2,1-a]isoquinoline.

90 g. of 2-phenyl-5,6-dihydro-8,9-dimethoxypyrrole [2,1-a]isoquinoline in 2.7 l. of alcohol are hydrogenated in an autoclave at 100°C. under a pressure of 130 atmospheres, in the presence of 30 g. of Raney nickel.

After 30 hours the hydrogenation is stopped, and the catalyst is filtered off hot and washed with hot alcohol. The solvent is evaporated under reduced pressure, the residue is taken up in 10% acetic acid and the solutoin is filtered.

2-Cyclohexyl-5,6-dihydro-8,9-dimethoxypyrrole [2,1-a]isoquinoline of melting point: 122° to 124°C. is obtained from the insoluble fraction by crystallisation from ethyl acetate.

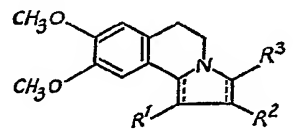
A precipitate of 2-cyclohexyl-1,2,3,5,6,10b-hexahydro-8,9-dimethoxypyrrole [2,1-a] isoquinoline is obtained from the acetic acid solution rendered alkaline with ammonia.

The product may be purified via the sulphate which is precipitated from ethyl acetate by sulphuric acid and recrystallised from alcohol-acetone, or via the hydrobromide perbromide obtained by means of bromine and hydrobromic acid in acetic acid.

2 - Cyclohexyl - 1,2,3,5,6,10b - hexahydro - 8,9 - dimethoxypyrrole [2,1-a]isoquinoline sulphate has a melting point of 170° to 171°C, and the hydrobromide perbromide a melting point of 146° to 148°C. The base melting point: 91° to 92°C. is obtained from these salts.

WHAT WE CLAIM IS:—

1. A pyrrole [2,1-a] isoquinoline derivative having the formula:



(I)

in which the pyrrole ring may be unsaturated or saturated, R^1 is a hydrogen atom or a carboxyl or esterified carboxyl group, R^2 is an alkyl, cycloalkyl, aryl, carboxyl, esterified carboxyl, carboxymethyl, esterified carboxymethyl, carboxyamido or substituted carboxyamido group, R^3 is a hydrogen atom or a carboxyl or esterified carboxyl group, or R^2 and R^3 when taken together may form the anhydride group of the corresponding dicarboxylic acid, and salts and addition compounds with pharmacologicaly acceptable organic or inorganic bases or acids.

2. 2 - Phenyl - 5,6 - dihydro - 8,9 - dimethoxypyrrole [2,1-a] isoquinoline - 1-carboxylic acid.

3. Ethyl 2 - phenyl - 5,6 - dihydro - 8,9 - dimethoxypyrrole [2,1-a] isoquinoline-1-carboxylate.

4. Dimethylaminoethyl 2 - phenyl - 5,6 - dihydro - 8,9 - dimethoxypyrrole [2,1-a] isoquinoline-1-carboxylate.

5. 2 - Phenyl - 5,6 - dihydro - 8,9 - dimethoxypyrrole[2,1-a]isoquinoline.

6. 2-Cyclohexyl-5,6-dihydro-8,9-dimethoxypyrrole[2,1-a]isoquinoline.

7. 2 - Phenyl - 1,2,3,5,6,10b - hexahydro - 8,9 - dimethoxypyrrole [2,1-a] isoquinoline.

8. 2 - Cyclohexyl - 1,2,3,5,6,10b - hexahydro - 8,9 - dimethoxypyrrole [2,1-a] isoquinoline, and the sulphate and hydrobromide perbromide thereof.

9. 5,6 - Dihydro - 8,9 - dimethoxypyrrole [2,1-a]isoquinoline - 2 - carboxylic acid.

10. Ethyl 5,6 - dihydro - 8,9 - dimethoxypyrrole [2,1-a] isoquinoline - 2-carboxylate.

11. 5,6 - Dihydro - 8,9 - dimethoxypyrrole [2,1-a] isoquinoline - 2 - carboxylic acid N,N-diethylaminoethylamide.

12. 5,6-Dihydro - 8,9 - dimethoxypyrrole [2,1-a] isoquinoline - 2,3 - dicarboxylic acid.

13. Diethyl 5,6 - dihydro - 8,9 - dimethoxypyrrole [2,1-a] isoquinoline - 2,3-dicarboxylate.

14. 5,6 - Dihydro - 8,9 - dimethoxypyrrole [2,1-a]isoquinoline - 2,3 - dicarboxylic acid anhydride.

15. 2 - (N,N - Diethylaminoethyl - carbamyl) - 5,6 - dihydro - 8,9 - dimethoxypyrrole [2,1-a]isoquinoline-3-carboxylic acid.

16. Dimethylaminoethyl 2 - methyl - 5,6 - dihydro - 8,9 - dimethoxypyrrole [2,1-a]isoquinoline-3-carboxylate, and the hydrochloride thereof.

17. γ - Piperidinopropyl 2 - methyl - 5,6 - dihydro - 8,9 - dimethoxypyrrole [2,1-a]isoquinoline-3-carboxylate.

18. 5,6 - Dihydro - 8,9 - dimethoxypyrrole [2,1-a]isoquinoline - 2 - acetic acid.

19. Ethyl 5,6 - dihydro - 8,9 - dimethoxypyrrole [2,1-a]isoquinoline - 2 - acetate.

20. A process for the preparation of a compound of formula (I) herein which comprises condensing a substituted α-halocarbonyl compound of the formula

$$R^3—CHX—CO—R^2,$$

wherein X represents a halogen atom, with an appropriately substituted 3,4-dihydro isoquinoline derivative, if desired, subjecting the cyclisation product so obtained to appropriate transformations of the substituent groups to obtain the desired compound of formula (I) and, if desired, subjecting the compound to catalytic hydrogenation to obtain the corresponding pyrrolidine compound.

21. A process according to claim 20, in which 1-methyl-3,4-dihydro-6,7-dimethoxy-isoquinoline is condensed wtih diethyl chloro-oxalacetate or ethyl chloropyruvate, or ethyl γ-chloroacetoacetate, respectively yielding the ethyl esters of 5,6-dihydro - 8,9 - dimethoxypyrrole [2,1-a]isoquinoline - 2,3 - dicarboxylic acid or 5,6-dihydro - 8,9 - dimethoxypyrrole [2,1-a]isoquinoline - 2 - carboxylic acid or 5,6-dihydro - 8,9 - dimethoxypyrrole [2,1-a]isoquinoline - 2 - acetic acid and thereafter the ethyl esters thus obtained are saponified with alkali yielding the corresponding acids.

22. A process according to claim 20, in which 5,6-dihydro-8,9-dimethoxypyrrole [2,1-a]isoquinoline-2,3-dicarboxylic acid is subsequently converted to the anhydride by dehydration and the latter is reacted with an amine to obtain a monoamide (particularly 2 - (N - diethylaminoethyl - carbamyl) 5,6 - dihydro - 8,9 - dimethoxypyrrole [2,1-a]isoquinoline-3-carboxylic acid) which, if desired, may be decarboxylated by heating to give 5,6-dihydro-8,9-dimethoxypyrrole [2,1-a]isoquinoline-2-carboxylic acid N-diethylaminoethylamide.

23. A process according to claim 20, in which 6,7-dimethoxy-3,4-dihydro-1-

methyl-isoquinoline is condensed with ω-bromoacetophenone and the resulting product is hydrogenated in the presence of a platinum-based catalyst to yield 2-phenyl-1,2,3,5,6,10b-hexahydro-8,9-dimethoxypyrrole [2,1-a]isoquinoline, or in the presence of Raney nickel to yield 2-cyclohexyl-1,2,3,5,6,10b-hexahydro-8,9-dimethoxypyrrole [2,1-a]isoquinoline and 2-cyclohexyl-5,6-dihydro-8,9-dimethoxypyrrole [2,1-a]isoquinoline.

24. A process according to claim 20, in which 6,7-dimethoxy-3,4-dihydro-1-methyl-isoquinoline is condensed with bromomethylcyclohexylketone, thereby obtaining 2 - cyclohexyl - 5,6 - dihydro - 8,9 - dimethoxypyrrole [2,1-a] isoquinoline.

25. A process according to claim 20, in which ethyl 6,7-dimethoxy-3,4-dihydro-isoquinoline-1-acetate is condensed with ω-bromoacetophenone and that thereafter the ethyl 2 - phenyl 5,6 - dihydro - 8,9 - dimethoxypyrrole [2,1-a] isoquinoline - 1-carboxylate is saponified to give the free acid.

26. A process according to claim 20, in which, when a compound having formula (I) wherein R^1, or R^2 or R^3 represent an esterified carboxyl group is obtained, it is converted into an ester containing a basic group by trans-esterification with an amino-alcohol.

27. A process according to claim 20, which, when a compound having formula (I) wherein R^1 or R^2 or R^3 represent an esterified carboxyl group is obtained, it is converted to an amide by reaction with an amine.

28. A pharmaceutical composition comprising, as the active ingredient, a compound of formula (I) herein, or a salt or addition compound thereof, in admixture with a pharmacologically acceptable carrier.

29. A pharmaceutical composition according to claim 28, which is in the form of tablets, capsules, dragees or suppositories or in the form of a solution or suspension which can be used orally or is injectable.

30. A process for the preparation of a compound of formula (I) herein substantially as hereinbefore described with reference to the Examples.

31. Pyrrole [2,1-a] isoquinoline derivatives of formula (I) herein whenever prepared by a process according to claim 30.

STEVENS, LANGNER, PARRY & ROLLINSON,
Chartered Patent Agents,
Agents for the Applicants.

Printed for Her Majesty's Stationery Office by the Courier Press, Leamington Spa, 1969.
Published by the Patent Office, 25 Southampton Buildings, London, W.C.2, from which copies may be obtained.